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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/853,033	05/11/2001	Pierre Chambon	065691-0222	5081

22428 7590 12/31/2003

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EXAMINER	
QIAN, CELINE X	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/853,033	CHAMBON ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-19,21-33 and 35-64* is/are pending in the application.

4a) Of the above claim(s) *9,13,15-18,21,22,24-32,35-49,51 and 53-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,2,4-8,10-12,14,19,23,33,50,52 and 62-64* is/are rejected.

7)☒ Claim(s) *33 and 52* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 September 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1, 2, 4-19, 21-33, 35-64 are pending in the Application. Claims 9, 13, 15-18, 21, 22, 24-32, 35-49, 51, 53-61 are withdrawn from consideration for being directed to non-elected subject matter. Claims 1, 2, 4-8, 10-12, 14, 19, 23, 33, 50, 52 and 62-64 are currently under examination.

This Office Action is in response to the Amendment filed on 10/6/03.

Response to Amendment

Acknowledgement is made of Applicant's submission of corrected drawings.

Acknowledgment is made of Applicant's submission of a certified copy of foreign priority document.

The objection to claims 2, 4, 5, 19 and 52 has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 2-4, 5, 20 and 34 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

The rejection of claims 1-5, 7, 8, 10-12, 14, 20, 33 and 34 under 35 U.S.C. 102 (a) has been withdrawn in light of the arguments provided in the Declaration submitted by Applicants.

Claims 1, 2, 4-8, 10-12, 14, 19, 23, 33 and newly added claims 63 and 64 stand rejected under 35 U.S.C. 112 1st paragraph (written description) for reasons set forth of the record mailed on and further discussed below.

Claims 12, 4-8, 10-12, 14, 19, 23, 33, 52 and newly added claims 62-64 stand rejected under 35 U.S.C. 112 1st paragraph (scope of enablement) for reasons set forth of the record mailed on and further discussed below.

Claims 1, 2, 4-5, 7, 8, 10-11, 19, 33 and newly added claims 62-64 stand rejected under 35 U.S.C. 112 102(b) paragraph for reasons set forth of the record mailed on and further discussed below.

The rejection of claims 6, 23 and 52 under 35 U.S.C. 103 (a) is maintained for reasons set forth of the record mailed on and further discussed below.

Claims 33 and 52 are objected to for reasons discussed below.

Claim 50 is rejected under 35 U.S.C.112 2nd paragraph for reasons discussed below.

Response to Arguments

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-8, 10-12, 14, 19, 20, 23, 33, 34 and newly added claims 63 and 64 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In response to the rejection, Applicants argue that one of skilled in the art would know what is meant by a natural or synthetic recombinase. Applicants further argue that the specification describes variants of the recombinase protein on page 10, lines 8-25, natural variants on page 13, lines 1-10, and a definition of nuclear receptor fragment on page 13, lines 19-21. Moreover, Applicants assert that a fragment can be identified by a LBD assay.

These arguments has been fully considered but deemed unpersuasive. As discussed in the previous office action, in analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure, next, it is to determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. The description Applicants refer to merely defines the functional activity of the natural or synthetic variants of the recombinase, or nuclear receptor fragment. However, the specification does not teach what is the common structure these variants must have to possess such function. As such, the structural functional relationship is missing. Therefore, the specification fails to describe the invention with a representative number of species by their complete structure and other identifying characteristics. Thus, the written description requirement is not met.

Claims 1-8, 10-12, 14, 19, 20, 23, 33, 34, 52 and newly added claims 62-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic mouse comprising a first transgene comprising Cre recombinase fused to a mutated ER, wherein such mutation result in conditional activation of Cre upon synthetic ligand treatment but not with natural ligand; a second transgene comprising insertion Cre recognition sites loxP flanking the gene of interest, wherein deletion of the gene exhibits transgene dependent phenotype, does not reasonably provide enablement for any transgenic mouse comprising a cell comprising claimed transgenes. Further, the specification does not enable any transgenic mouse without any phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

In response to the rejection, Applicants amended claims to read on a transgenic mouse. Applicants argue that the specification provides three working examples of said mouse. Therefore, the invention is enabled.

This argument has been fully considered but deemed unpersuasive. As discussed in the previous office action, the phenotype of the transgenic mouse is a critical element for the enablement of the claimed invention because one of skilled in the art would not know how to use a mouse with the claimed genotype but has no phenotype. The specification fails to teach how to use such a mouse. The state of art teaches that the phenotype of the transgenic mouse is unpredictable. Therefore, this rejection is maintained.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7, 8, 10-11, 19, 20, 33, 34 and newly added claims 62-64 are rejected under 35 U.S.C. 102(b) as being anticipated by Feil et al.

In response to this rejection, Applicants argue that Feil fails to teach that the chromosomal gene of interest, which is the target of excision, is endogenous to the mouse. Applicants argue that this is an essential feature of the present invention which is not anticipated by the Feil reference.

This argument has been fully considered, but it is not persuasive. Contrary to Applicant's assertion, the instant claims do not have the limitation of excise an endogenous target gene. The

claims recite "...one or more gene or intergenic DNA sequences of interest naturally belonging to said genome of said mouse into which one or more recognition sites of said recombinase protein are inserted, said DNA sequence of interest being located in one or more of the chromosomes of the genome of said cell." Such recitation only requires that he recombinant sites be inserted into the intergenic sequence or endogenous gene sequence of the host chromosome. Feil discloses a transgenic mouse with loxP sites inserted into the endogenous RXRα gene. Therefore, this limitation is anticipated by the Feil reference. Thus, this rejection is maintained.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Indra et al. and Feil et al., in view of Ross et al. and Tontonoz et al. (1997, PNAS, Vol.94, pp.237-241)

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Feil et al., in view of Schwenk et al.

In response to this rejection, Applicants describes the instant invention as following: "The instant invention provides a general method for efficient stage- and tissue-specific modification of a given gene in the living mouse. At the time of filing applicants provided examples for such modifications in three cell populations (keratinocytes, adipocytes and hepatocytes) of three distinct organs using different transgenic mice expressing fusion proteins.

Each of the fusion proteins contain a modified estrogen receptor ligand binding domain (ER^T, ER^{T2}) conferring in vivo tamoxifen-inducibility to the activity of the fused Cre recombinase. Transgenic lines were then bred with mice in which endogenous genes, in their normal chromosomal position and environment, contain engineered LoxP sites specifically recognized by a Cre recombinase. In the progeny, the fused Cre recombinase is activated upon tamoxifen treatment and specifically deletes gene segments flanked by LoxP-sites. In each case, the deletion was 100% efficient in all cells in which the recombinase was expressed. Moreover, a deletion was not observed in the absence of tamoxifen treatment, indicating that the inventive method permits tight temporal control of the generation of cell type/tissue-specific somatic mutations." Applicants argue that Feil and Indra only demonstrated that Cre-ER^T or Cre-ER^{T2} fusion proteins could be used to delete DNA segments within synthetic reporter transgenes. Applicants further argue that the tamoxifen-induced Cre-ER fusion protein taught by Schwenk et al. cannot be used to delete a chromosomal segment of DNA with an efficiency to validly study gene function. Lastly, Applicants argue that Tontonoz et al. do not relate to the technical field of the claimed invention. Applicants thus conclude that the claimed invention is not obvious in view of the combined teaching of the cited references.

These arguments have been fully considered but deemed unpersuasive. The teaching of the references and the reasons for the obviousness of the claimed invention were discussed in detailed in the previous office action (see pages 13-16). Applicants are reminded that the claimed invention is drawn to a transgenic mouse having in its genome a fusion protein comprising a recombinase, a hinge region and a ligand binding domain of human ER, and recombinase sites inserted into the intergenic or endogenous gene sequences of the host genome.

The specific feature described by the Applicants is not part of the limitation of the claims. In addition, Feil teaches the insertion of the recombinant sites into an endogenous gene, RXRα. Therefore, the combined references teach all the limitations of the claims. For reasons discussed in the previous office action, the claimed invention is obvious in view of the combined teaching of the cited references.

The Declaration by Applicant has been fully considered. Similarly, the Declaration describes the instant invention as a general method for efficient stage- and tissue-specific modification of a given gene in the living mouse. Applicant asserts that the deletion was 100% efficient in all cells in which the recombinase was expressed. Moreover, a deletion was not observed in the absence of tamoxifen treatment, indicating that the inventive method permits tight temporal control of the generation of cell type/tissue-specific somatic mutations. Applicant asserts that this method is not anticipated by the combined references because none of the references teaches the advantage of the 100% efficiency. However, these arguments are not persuasive for same reasons discussed above (claims do not recite such limitation). Therefore, this rejection is maintained.

New Grounds of Rejection

Claim Objections

Claims 33 and 52 are objected to as being dependent upon a non-elected base claims (25 and 30).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 recites the limitation "said RXR_{α}" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 703-305-1998. The fax phone number for the organization where this application or proceeding is assigned is 703-305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER